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Perceived medication adverse effects and coping strategies reported by chronic heart failure patients

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SUMMARY

Background: Data on medication adverse effects (AEs) in chronic heart failure (CHF) are primarily based on results from clinical trials. Little is known about AEs perceived by CHF patients in daily practice and how patients deal with these subjective AEs. **Aims:** To describe the scope and nature of perceived AEs of CHF patients, their coping strategies and the relationship of perceived AEs to medication, patient characteristics and quality of life. **Methods:** This cross-sectional observational study included a sample of 680 patients previously hospitalised for CHF. Perceived AEs and coping strategies were collected by interviews based on a structured questionnaire. Medication and clinical information were collected by chart review. **Results:** Of the 670 CHF patients completing the questionnaire, 17% reported at least one AE. In total, 186 AEs were reported of which 15% could not be linked to any medication. Nausea (4%), dizziness (4%), itches (3%) and rash (3%) were the most prevalent. The drug associated with the highest AE rate was pravastatin (27%). On average, more than five different drugs could be related to the AEs headache, dizziness and nausea. Patients reporting AEs had a lower general health perception, younger age and were more often using antiarrhythmic drugs. Of patients experiencing AEs, 69% conferred with their doctor, 24% reported having done nothing in reaction and 2% discontinued their medication without discussing it with the doctor. **Conclusion:** Adverse effects are frequently perceived by CHF patients, but they are difficult to recognise and manage in daily practice.

What's known

- Data on drug safety are primarily based on the results from clinical trials, where the patients included often have less comorbidity and comedication than the patients using the drugs in everyday practice.
- It has been estimated that at least 5–10% of patients in clinical trials discontinue use of placebo because of perceived adverse effects (AEs).
- Perceived AEs are often reported as a common reason for non-adherence in CHF.
- Patient characteristics associated with AEs of medication are the number of coexisting conditions and the number of concurrently used medications.

What's new

- The overall rate of AEs reported by patients of 17% is higher than detected by reports from healthcare providers or observed in clinical trials.
- Socio-demographic and clinical variables have little capability in predicting the risk of perceiving AEs in patients with CHF.
- Up to one-third of the patients experiencing an AE did not communicate the AE with the healthcare provider.
- Perceived AEs may be attributed to several different medications, underlining the complexity of managing AEs in CHF.

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Disclosures
None.

Introduction

Chronic heart failure (CHF) is a disabling progressive condition, which is a significant problem for both those suffering from the disease and the healthcare professional. Over the past few decades, tremendous gains have been achieved both in pharmacological and in technological treatment for patients with CHF. As a result, CHF patients are commonly exposed to a lifelong treatment with multiple drugs, often requiring inconvenient medication schedules and frequent changes in treatment. It has been shown that adequate drug treatment is associated with fewer cardiovascular hospitalisations (1), but polypharmacy may also cause more drug-induced adverse events as well as more drug-drug interactions (2). Because of older age, CHF patients are also at higher risk for experiencing adverse drug events because of age-associated changes in pharmacokinetics and pharmacodynamics (2,3).

There is little information available regarding adverse effects (AEs) perceived by CHF patients in daily practice. Data on drug safety and more in particular, on adverse drug events of CHF patients are primarily based on results of randomised clinical trails. These commonly reflect objectively evaluated adverse events in a selective patient population, which are likely to differ from the subjective AEs patients may experience in everyday practice. Evidence is emerging that adverse drug events are often

inadequately reported in clinical trials (4). The reported prevalence of common physical symptoms, such as headache or fatigue, is usually much lower in clinical trials than would be expected from epidemiological survey data (5). Additionally, clinical trials often include patients with less comedication, comorbidities and other conditions that may increase the perceived AEs in comparison to patients using the drugs in everyday practice.

In daily practice, however, perceived AEs have been reported as a common reason for non-adherence in CHF (6,7). This may lead to decompensation requiring emergency hospitalisation (8,9) and to increased mortality and morbidity rates, impaired quality of life and increased healthcare costs (10). On the other hand, patients may also decide to continue taking a drug despite perceived AEs. Little is known about the different coping strategies the CHF patients may use to manage the perceived AEs of medication.

To improve the management of adverse drug effects, it is important to increase the knowledge about the extent and nature of AEs as perceived by CHF patients in daily practice and the strategies they use to cope with them. We conducted this study with the following purposes:

(1) To describe the proportion and type of perceived AEs of CHF patients and their possible relationship to the medication used;
(2) To describe demographic and clinical characteristics of CHF patients who perceive AEs;
(3) To describe strategies undertaken by CHF patients in response to the perceived AEs.

Methods

Patient population

Patients in this study were participants in the Coordinating study evaluating Outcomes of Advising and Counselling in heart failure (the COACH study). This was a multicentre randomised controlled trial designed to determine the effect of education and counselling in CHF patients. The design and results of the study are described elsewhere (11,12). Patients were recruited in the COACH study between October 2002 and February 2005. To be eligible, patients needed to be hospitalised for symptomatic heart failure (HF) [New York Heart Association Classification (NYHA) II–IV], had to be older than 18 years and had to have evidence of structural underlying heart disease. Patients were excluded, if they underwent invasive procedure or cardiac surgery intervention within the last 6 months or planned to be performed within the next 3 months; were unable to complete questionnaires; were included in another concurrent study or HF clinic or were unable or unwilling to give informed consent.

Design and data collection

After written informed consent, patients randomised to the experimental groups (n = 680) of the COACH study were interviewed during the index hospitalisation (= baseline) by a HF nurse using a structured questionnaire, which included questions about perceived AEs. We conducted a cross-sectional observational study of this baseline survey. Ethical approval was gained from the Central Ethics Committee and the investigation conformed to the principles outlined in the Declaration of Helsinki.

Perceived adverse effects

Perceived AEs of medication were assessed by asking first a filter question: 'Do you experience any adverse effect of your medication? (yes/no)'. Next, a drug-related symptom list was given with the following potential adverse drug events: nausea, dizziness, problems with sleep, headache, rash, itching, impotence, cough, cold extremities and constipation. Patients were also given the opportunity to specify any other AE they experienced which was not on the list.

Undertaken actions

Patients who reported any AE were asked which action they had undertaken in response to the experienced AE. Possible answers provided were: doing nothing, discussing it with the doctor, decreasing the dose of the medication, discontinuing the medication or other actions besides those listed.

Potentially related medication

Information about medication therapy taken at discharge was collected by chart review. Medications were categorised as 'potentially related' to an AE, if the reported AE was consistent with the known AE profile of that particular medication according to the Dutch Drug Compendium (Farmacotherapeutic Kompas). Reported AEs that could not be related to any medication taken were categorised as 'improbable'.

Demographic and clinical data

Data on demographic and clinical variables were collected by patient interviews and review of medical records. Demographic data included age, gender, living status (living alone or not) and educational level (no education/primary school, secondary school and higher education/university). Quality of life was assessed with the validated Medical Outcome Study

36-item General Health Survey (RAND-36), a self reported generic questionnaire of general health status. Clinical variables consisted of duration of heart failure, left ventricular ejection fraction (LVEF), NYHA functional class at discharge (II–IV), aetiology of HF, measurements of blood pressure (BP), serum electrolytes and estimated glomular filtration rate (eGFR) at discharge, number of comorbidities (as categorical variable: 0, 1–2, 3–4, ≥ 5 comorbidities) and presence of specific comorbidities (vascular disorders, respiratory disorders, diabetes, gastrointestinal disorders, stroke, renal/urinary disorders, musculoskeletal disorders and/or neoplasms).

Statistical analysis

Continuous variables are summarised as mean value ± standard deviation and categorical data are presented as percentages. For the most commonly used medication classes, potentially related AEs are reported in absolute numbers and percentages. Data are only presented for those medications taken by at least 10 patients. For the descriptive analysis as well as univariate and multivariate analyses, medication was grouped at therapeutic level. For the antiarrhythmic agents, this includes only class I and III antiarrhythmics.

Differences in demographic and clinical characteristics between reporters of AEs and non-reporters were tested with χ^2 tests or Fisher's exact tests for dichotomuous variables. Two-tailed *t*-tests were used for normally distributed data and the Mann–Whitney *U*-test for non-parametric data. Furthermore, we tested for differences in BP, serum electrolytes and eGFR between reporters and non-reporters of specific AEs. In more detail, we looked for BP, sodium and potassium as a proxy for headache and dizziness and for eGFR as a proxy for itches. Multivariable logistic regression analysis was conducted to investigate the relationship of variables found to be significant in the univariate analysis. All data were analysed using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA).

Results

Sample characteristics

Of the 680 patients, 670 patients provided data during the interview. The mean age was 70 years, 63% were men and 55% had no education or only primary school (Table 1). Over 43% of the patients had NYHA Class IV at admission and the mean LVEF was 33% (± 14%). The main aetiology of HF was ischaemic heart disease. A majority of patients received diuretics and angiotensin converting enzyme (ACE)-inhibitors; beta-blockers were used by 66%, anticoagulants by 62% and lipid-lowering agents by 39%, including 37% using statins (Table 1).

Perceived adverse effects

Of the 670 patients who completed the questionnaire, 116 patients (17%) reported at least one AE of medication, resulting in a total of 186 AEs that patients related to their medication (Table 2). The number of reported AEs ranged from 1 to 6 per patients; 44 patients reported two or more different AEs. The most prevalent reported AEs were dizziness, nausea, itches and rash. Cough was reported by only 1.5% of the patients in this sample. Patients experienced a wide variety of other AEs besides those listed with the most frequently being other gastrointestinal problems, dry mouth and less appetite.

Potentially related medication

Of the 186 reported AEs, 28 (15%) were classified as improbable, meaning that the reported AEs could not be related to any medication taken. The most commonly 'improbable' reported AEs were itches and impotence, which were reported by seven and three patients, respectively, who did not take any medication that could be linked with itches and impotence. In total, 52 different classes of medication could be related to the remaining 158 reported AEs. Rates of potentially related AEs for commonly prescribed cardiovascular and antithrombotic medication, i.e. prescribed to more than 10 patients in our study population, ranged from 3 to 27% (Table 3). Medications with high rates were pravastatin, dipyridamol, ramipril and amlodipine. Pravastatin was the third most commonly prescribed agent within the drug class lipid-lowering agents, being prescribed to 60 patients, respectively (Table 3). Ramipril, amlodipine and dipyridamol were prescribed to 62, 40 and 12 patients, respectively.

Most drugs were related to several AEs, with pravastatin, atorvastatin and metoprolol being the drugs related to at least six different AEs. Nausea was found in combination with all included medication classes except angiotensin receptor blockers (ARBs). Dizziness was common for all antihypertensive and lipid-lowering agents. Adverse effects, such as headache, rash, sleeping problems and constipation showed no consistent relation with a specific medication class. Itches were observed in relation to ACE-inhibitors but more frequently in relation to other medications not included in Table 3, such as salmeterol, oral blood glucose lowering medication and proton-pump-inhibitors. Adverse effects that can be uniquely linked to a drug class, i.e. cough for ACE-inhibitors and ARBs and cold extremities for beta receptor blockers, were reported by up to 7% of

Table 1 Demographic and clinical characteristics of the HF population

	n = 670
	% or mean ± SD
Demographics	
Age (years)	70.4 ± 11.5
Gender (female)	37
Educational Level	
No education/ primary school	55
Secondary school	27
Higher education/university	17
Living alone	39
Clinical characteristics	
Duration of heart failure (years)	1.5 ± 3.4
LVEF (%)	33.5 ± 14.4
NYHA(at admission)	
II–III	57
IV	43
Aetiology of HF	
Ischaemic HF	43
Non-ischaemic HF	57
Comorbidities	
No comorbidities	18
1–2 comorbidities	54
3–4 comorbidities	24
≥ 5 comorbidities	4
Vascular disorders	56
Respiratory disorders (COPD/Asthma)	31
Diabetes	28
Gastrointestinal disorders	13
Stroke (CVA – TIA)	17
Renal and urinary disorders	8
Musculoskeletal disorders	8
Neoplasms (benign, malignant)	4
Medication burden	7.5 ± 2.8
Heart failure medication (at discharge)	
ACE-inhibitors	74
ARBs	11
Beta-blockers	66
Cardiac glycosides	30
Diuretics	96
High-ceiling diuretics	88
Potassium sparing diuretics	
Spironolactone	51
Triamterene	1
Other medication	
Calcium channel blockers	15
Nitrates	31
Alfa-1-receptorblocker	1
Lipid-lowering agents	39
Antiplatelet drugs	33
Anticoagulants	62
Antiarrhythmic agents*	11
Antianginals agents	0.5

Data are presented as mean ± SD or in percentages. *Antiarrhythmic agents include class 1 and III antiarrhythmics. COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Classification; ARBs, angiotensin receptor blockers; HF, heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Table 2 Reported adverse effects

Adverse effects	*n* (%)
Nausea	26 (3.9%)
Dizziness	25 (3.7%)
Itches	17 (2.5%)
Rash	17 (2.5%)
Cold extremities	12 (1.8%)
Cough	11 (1.6%)
Impotence	9 (1.3%)
Headache	8 (1.2%)
Sleep disturbance	7 (1.0%)
Constipation	4 (0.6%)
Others	50 (7.5%)
Total number of reported AEs	186

AEs, adverse effects.

patients using these drugs. In 50% of the cases, patients were already using these drugs for more than 1 month, with a mean use of 1258 days (± 1940).

For patients reporting headache, nausea or dizziness, on average, more than five different medications could be related to these AEs (Figure 1). In one case, a patient used 11 different medications that could all be linked to the reported AE 'nausea'.

Factors related to perceived adverse effects

Patients reporting AEs had a lower general health perception compared with patients not reporting AEs (Table 4). On the other eight subscales, representing other dimensions of quality of life, there were no significant differences. Furthermore, patients reporting AEs were younger than non-reporters and patients on antiarrhythmics reported more often AEs. None of the other demographic or clinical factors was found to be associated in the univariate analysis. In the multivariate logistic regression, age (OR = 0.98, 95% CI: 0.96–0.99), antiarrhythmic drug use (OR = 2.29, 95% CI: 1.29–4.05) and general health

Table 3 Cardiovascular and antithrombotic drugs potentially related with perceived adverse effects. (no. of related events %)*

Medication	Any AE no. of related events/total no. of prescriptions (%)	Nausea	Rash	Dizziness	Headache	Impotence	Cough	Sleep problems	Constipation	Cold extrimities	Itches	Other AE
Antithrombotics												
Acenocoumarol	20/363 (6)	14 (4%)										6 (2%)
Carbasalaatcalcium	20/155 (13)	3 (2%)	5 (3%)	5 (3%)	3 (2%)							4 (3%)
Clopidogrel	4/24 (17)	1 (4%)			2 (8%)							1 (4%)
Dipyridamol	3/12 (25)	1 (8%)	1 (8%)									1 (8%)
Fenprocoumon	4/40 (10)	4 (10%)										
Heartglycosides												
Digoxine	26/199 (13)	9 (5%)		8 (4%)	3 (2%)							6 (3%)
ACE-inhibitors												
Captopril	2/62 (3)		2 (3%)									
Enalapril	13/93 (14)	5 (5%)		3 (3%)	1 (1%)		2 (2%)					2 (2%)
Fosinopril	15/70 (21)			6 (9%)	1 (1%)		2 (3%)		1 (1%)		3 (4%)	2 (3%)
Lisinopril	9/64 (14)	3 (5%)		2 (3%)	2 (3%)	1 (2%)	1 (2%)					
Perindopril	6/91 (7)					1 (1%)		1 (1%)			2 (2%)	2 (2%)
Quinapril	4/26 (15)	1 (4%)										3 (12%)
Ramipril	14/62 (23)	3 (5%)		5 (8%)	1 (2%)		2 (3%)				2 (3%)	1 (2%)
ARBs												
Candesartan	1/16 (6)			1 (6%)								
Losartan	6/41 (15)			2 (5%)			3 (7%)					1 (2%)
Beta-blockers												
Atenolol	1/25 (4)									1 (4%)		
Bisoprolol	10/86 (12)			4 (5%)	1 (1%)			1 (1%)		2 (2%)		2 (2%)
Carvedilol	9/91 (10)	1 (1%)		5 (5%)	1 (1%)					1 (1%)		1 (1%)
Metoprolol	35/182 (19)	6 (3%)	6 (3%)	3 (2%)	2 (1%)			5 (3%)	2 (1%)	6 (3%)		5 (3%)
Sotalol	3/31 (10)			2 (6%)		1 (3%)						
Calcium channel blockers												
Verapamil	1/21 (5)			1 (5%)								
Diltiazem	2/21 (10)			1 (5%)	1 (5%)							
Amlodipine	9/40 (23)	2 (5%)	2 (5%)	2 (5%)		2 (5%)						1 (3%)
Lipid-lowering agents												
Atorvastatine	15/68 (22)	5 (7%)	4 (6%)	2 (3%)	1 (1%)	2 (3%)			1 (1%)			
Simvastatine	10/108 (9)	3 (3%)		2 (2%)	3 (3%)							2 (2%)
Pravastatine	16/60 (27)	3 (5%)	2 (3%)	5 (8%)	1 (2%)			1 (2%)	1 (2%)			3 (5%)
Antiarrhythmic agents†												
Amiodaron	13/64 (20)	2 (3%)	4 (6%)		2 (3%)	2 (3%)		3 (5%)				
Diuretics												
Bumetanide	12/305 (4)			9 (3%)								3 (1%)
Furosemide	21/283 (7)			15 (5%)								6 (2%)
Spironolactone	31/343 (9)	13 (4%)		13 (4%)		3 (1%)						2 (1%)
Nitrates												
Nitroglycerine oromusc	2/21 (10)			1 (5%)								1 (5%)
Nitroglycerine transd	1/18 (6)	1 (6%)										
Isosorbide-5-mononitrate	10/144 (7)	5 (3%)		3 (2%)	2 (1%)							
Isosorbidenitrate	7/54 (13)	4 (7%)		2 (4%)	1 (2%)							

*A medication was excluded if fewer than 10 patients were taking that medication. †Antiarrhythmic agents include class I and III antiarrhythmics. AE, adverse effect; ARBs, angiotensin receptor blockers.

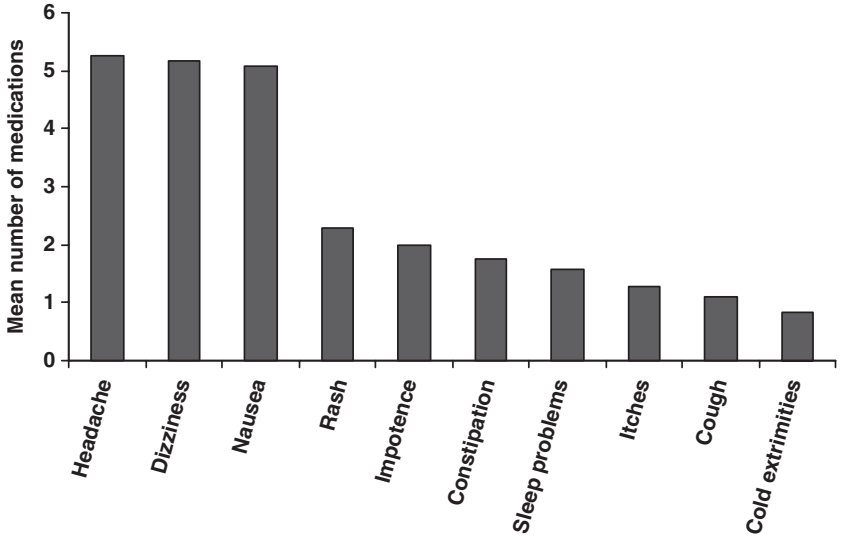

Figure 1 Mean associated medication per reported adverse effect within one patient

perception (OR = 0.98, 95% CI: 0.97–0.99) were all identified as independent predictors of perceiving AEs in CHF patients. No significant differences were seen between patients reporting specific AEs and the other patients regarding BP, serum electrolytes or eGFR (data not shown).

Undertaken actions

Of patients experiencing an AE, 69% discussed this with the doctor and 24% reported having done nothing in reaction. Four patients (3%) discontinued the medication, half of whom having not discussed the AE with their doctor. None of the patients reported having reduced the dose of their medication (Figure 2). Eleven patients (9%) reported another strategy to deal with the experienced AE, such as discussing the AE with the HF nurse or taking additional medication to alleviate the symptoms (e.g. skin cream or analgesics).

Discussion

To our knowledge, this is the first survey examining perceived AEs of medication in a cohort of CHF patients. This study shows that one out of six CHF patients may perceive AEs of medication, with the most prevalent being nausea, dizziness, itches and rash. Besides the listed AEs, CHF patients reported a high number of other perceived AEs. Although some AEs appeared to be related to specific medication classes, the relation between the most reported AEs and medication was diffuse. For the most commonly experienced AEs, at least five drugs per patient could be identified as being potentially related. Of the 186 reported AEs, 15% could not be linked to any medication taken. There were only a few differences in clinical and demographic characteristics between reporters and non-reporters of AEs, but reporters did have a lower general health perception. Finally, one-third of the patients appeared not to have communicated the perceived AE with their healthcare provider.

The observed overall rate of AEs of 17% in this study is similar to that seen in the survey studies in other patient groups (13,14), but higher than that detected in an observational study that did not use patient reports but a combination of review of hospital discharge notes, computer-generated signals and reports from healthcare providers (15). Looking at specific medication, rates were also higher than those observed in clinical trials with these drugs, where AEs were reported in around 10% or less patients (16,17). This can be explained by several reasons. First, in clinical trials, a commonly used parameter of safety reporting is the number of withdrawals or discontinuations of study treatment because of AEs (4,16). In our study, as in other surveys, AEs are those perceived by patients regardless of their consequences for treatment continuation. Second, there are differences between patients enrolled in trials and those in actual practice. Patients in this sample are exposed to complex medication regimens. Several studies showed an increase in AEs when the study medication is taken in patients with background medication (18) or when multidrug therapies are initiated (16). Finally, it has been suggested that patients participating in medication trials are healthier and have a higher tolerance for AEs and more positive drug attitudes compared with patients in clinical practice (5). When looking at individual

Table 4 Differences in demographic and clinical variables by adverse effects for reporters and non-reporters

	Reporters (n = 116)	Non-reporters (n = 554)	p-value
Demographics			
Age (years)	68 ± 12	71 ± 11	0.010*
Gender (female)	38%	36%	0.74
Educational level			
No education/primary school	64%	53%	0.72
Secondary school	24%	28%	
Higher education/university	12%	18%	
Living alone	37%	39%	0.75
RAND-36			
General Health Perception†	38 ± 18	45 ± 19	0.001
Clinical characteristics			
LVEF (%)	35 ± 15	33 ± 14	0.43‡
NYHA (at discharge)			
II–III	97%	97%	0.50
IV	3%	3%	
Duration of heart failure (years)	2.5 ± 3.7	2.7 ± 4.4	0.36‡
Number of comorbidities	1.9 ± 1.5	1.8 ± 1.4	0.71‡
Comorbidities			
Diabetes	24%	28%	0.42
Hypertension	46%	41%	0.31
COPD	32%	26%	0.18
Gastrointestinal disorders	12%	13%	0.75
Stroke (CVA – TIA)	16%	14%	0.56
Renal and urinary disorders	12%	7%	0.06
Medication burden	7.7 ± 2.8	7.4 ± 2.8	0.41*
HF Medication at discharge			
ACE-inhibitors	69%	75%	0.15
ARBs	15%	10%	0.08
Beta blockers	65%	67%	0.80
Diuretics	97%	96%	0.80
Digoxine	31%	30%	0.85
Other medication			
Calcium channel blockers	17%	14%	0.38
Nitrates	32%	31%	0.88
Alfa-1-receptorblocker	1%	1%	0.10
Lipid-lowering agents	45%	37%	0.12
Antiplatelet drugs	30%	33%	0.53
Anticoagulants	65%	61%	0.34
Antiarrhythmic agents§	20%	9%	0.001
Antianginals agents	1%	0.5%	0.43

* T-test for continuous variables. †Score between 0–100 and a higher score represent better health. ‡Non-parametric test: Mann–Whitney U-Test. Two-tailed Fisher's exact test or χ^2 test for binomial variables. §Antiarrhythmic agents include class I and class III antiarrhythmics. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Classification; COPD, chronic obstructive pulmonary disease; ARBs, angiotensin receptor blockers; CVA, cerebrovascular accident; TIA, transient ischemic attack.

drugs, pravastatin was found to be the drug most associated with reported AEs in our study. This is of interest given to the recent discussion about the value of statins in older patients with moderate-to-severe heart failure following from the results of the CORONA trial (19). However, one should keep in mind that the most commonly reported AEs for pravastatin (nausea and dizziness) are often also linked to alternative drugs.

In our study, on average, more than five different medications in one patient could be associated to the reported AEs such as headache, dizziness and nausea. Polypharmacy is a well-recognised problem in elderly people (20) as in CHF patients (21). Consequently,

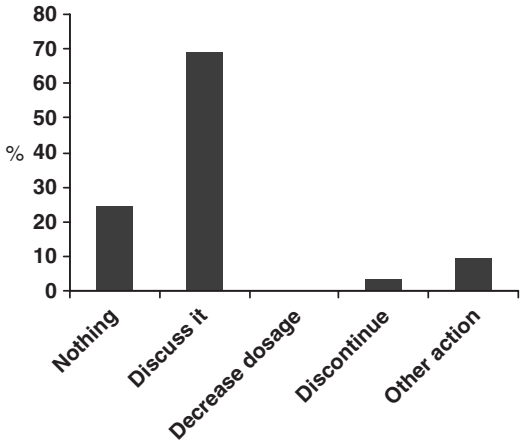

Figure 2 Actions undertaken by patients in response to perceived adverse effects

both evaluation of reported AEs and identification of the causal agent become a complex task in clinical practice. Research suggests that CHF patients have difficulty in differentiating heart failure symptoms from adverse drug events (22). Our study, however, shows that most of the perceived AEs could be attributed to the drug therapy used. Although we cannot make a causality assessment in this cross-sectional study, this implies that they could represent valid drug-symptom associations. Many patients experiencing dizziness used one or more drugs that may cause orthostatic hypotension. Patients experiencing cold extremities were almost all using beta blocking agents. Cough, thought to be frequently experienced in patients with heart failure by healthcare professionals in daily practice, however, was only reported by 1.5% of the patients in this sample. In all but one case, these were patients using ACE-inhibitors or ARBs. On the other hand, it is likely that some of the reported AEs are not caused by a drug. This phenomenon also occurs in clinical trials, where patients discontinue taking placebo because of medication-attributed AEs (5). In our study, 15% of the reported AEs were classified as improbable as they could not be related to any medication.

In this study, patients who reported an AE scored lower on the general health perception dimension of the RAND-36. Although the impact of 'minor' AEs on quality of life may be underestimated in clinical practice, they can cause additional worries and discomfort (23). We expect that perceived AEs can have an impact on the general health perception of patients (24). However, we cannot exclude that patients with a more negative health perception are more susceptible to perceiving AEs. Furthermore, using an antiarrhythmic drug regimen and younger age were also associated with reporting of AEs. Amiodarone is the most commonly prescribed antiarrhythmic drug and known for many potential AEs (25,26). The finding that younger age was related to perceiving more AEs was somewhat surprising, although studies in other patient groups also did not find any relationship between patient characteristics, such as age, gender, educational level, number of coexisting conditions, number of medications and rates of reported AEs (13,27). These findings are in contrast with studies looking at documented or verified adverse drug events that did show associations with age, number of comorbidities and number of medications in different populations (20,28,29). These disparate results suggest that although the risk of developing specific adverse drug events can be higher in certain patient populations, in patients with CHF socio-demographic and clinical variables have little capability in predicting the risk of perceived AEs. A possible explanation could be that most of the patients in our CHF cohort are rather old (on average 70 years), with multiple comorbidities and using many drugs and are therefore all at increased risk for experiencing AEs (27).

Studies focussing on factors influencing compliance behaviour in CHF identified AEs as one of the barriers to medication adherence (6,7). However, patients in our study did not report decreasing their dosage and only a few discontinued their medication because of experiencing an AE. This low rate could partly be because of our method of assessment, which was based on patient self-report and may therefore underestimate the true prevalence of non-compliance (30–32). On the other hand, heart failure is known to be associated with high mortality and with a high symptom burden. Therefore, these patients might be willing to endure certain AEs. Despite the low translation of symptom burden in non-compliance, the importance and value of these 'subjective' reported AEs remain. Indeed, the most perceived AEs are symptoms that do not endanger the health of the patient severely and may therefore not be taken seriously from a medico-technical point of view. However, from the patient perspective, these medically-minor symptoms may add substantially to the disease burden and cause subjective distress (23).

In our study, 71% of the included CHF patients discussed perceived AEs with a healthcare professional. This is consistent with the other studies showing 69% up to 85% of patients who communicated their concerns with a healthcare professional (14,33). The failure to discuss medication problems with the physician can result in ameliorable and preventable adverse drug events (14). Possible explanations for this failure to communicate can be that patients do not want to bother their physician, consider the

perceived symptoms as an unavoidable phenomenon of ageing or they find a way to manage certain AEs and accept them. Managing perceived AEs in clinical practice, therefore, seems to be best served by an individualised approach in face-to-face encounters with the healthcare professional. This patient-centred approach is considered a cornerstone of care (34). By nurse or doctor interaction, patients can be made more aware of potential AEs at the moment a new drug is initiated. This may contribute to good patient compliance and may facilitate early recognition of AEs.

This study is the first in describing perceived AEs in CHF and has some limitations. The cross-sectional nature of the design precludes any attempt to establish the direction of causality. Although we excluded cases where the medication was started after the AE report, we could not perform a causality assessment based on the exact timing of events. We acknowledge the possibility that some of the reported AEs may be the result of heart failure or other concurrent diseases rather than of the medication itself. However, patients themselves reported these as AEs of their medication and one should keep in mind that the subjective perceived AE by patients can be as important to adherence, distress and quality of life as when the association between the drug and the effect is objectively confirmed. Secondly, perceived AEs were determined by using an open-ended question as filter followed by a checklist of potential adverse drug events. In the literature, there is no consistency or gold standard as regards how to elicit perceived AEs. Open questioning can underestimate patients' experiences of perceived AEs (35). On the contrary, symptom checklists can increase the number of reported AEs by suggestion and are therefore likely to have low specificity for detecting true adverse drug events (35). However, our results as well as those from another study showed that patients are most likely to report symptoms which could be related to a high probability to medicines and are in line with the known AE profiles of the drugs prescribed (36). Because of relatively small numbers of patients reporting specific AEs, the power to detect differences in potentially related measurements of BP, serum electrolytes or eGFR was low. Finally, this study was conducted in a patient population that had been hospitalised for heart failure. This may have influenced the rate of reported AEs as patients could have been exposed to higher numbers of recent medication modifications than in an ambulatory setting.

This study underlines the complexity of recognising and managing adverse drug events in daily practice for CHF patients, as the most prevalent reported AEs could be related to at least four different drugs. As it is difficult to predict who will perceive an AE and not all patients will mention the AEs themselves, health professionals need to actively ask for and discuss AEs with the CHF patients. Retrieving additional information on the chronology of onset as well as the severity can help select the most fitting among alternative options to ameliorate, counter or cope with the AE.

Author contributions

R.H.E. De Smedt: formulated the concept of the study, data analysis and performed statistical analysis, interpretation of the results, drafting/writing and approval of the article. P. Denig: formulated the concept of the study, interpretation of the results, performed codrafting of the article, critical revision and approval of the article. F.M. Haaijer-Ruskamp: formulated the concept of the study, performed interpretation of the results, critical revision and approval of the article. T. Jaarsma: designed the concept of the study, performed interpretation of the results, critical revision and approval of the article.

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